Oxidative Coupling

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Copper-Catalyzed Oxidative C–O Coupling by Direct C–H Bond Activation of Formamides: Synthesis of Enol Carbamates and 2-Carbonyl-Substituted Phenol Carbamates**

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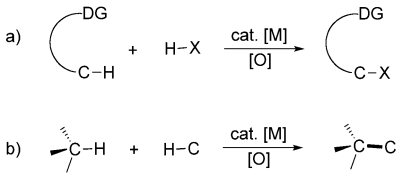
Coupling chemistry is an important synthetic strategy, widely used in both industry and academia for the formation of carbon–carbon and carbon–heteroatom bonds.[1] The traditional coupling procedures involve either the use of stoichiometric organometallic reagents, such as Grignard and organolithium reagents, or the transition-metal-catalyzed coupling of functionalized hydrocarbons. There has been substantial progress in these methods over the last few decades, and they are successfully applied in the synthesis of commercially important products.[2] However, the use of prefunctionalized starting materials in these methods, thus adding steps towards the formation of desired chemical bond, is a major concern for the synthetic chemist from an atom-economical and environmental point of view. The best way to address this issue is to utilize unfunctionalized starting materials by the direct activation of C–H bonds. Several reports have appeared in the literature on transition-metal-catalyzed C–H bond activation and its further application to carbon–carbon and carbon–heteroatom bond formations.[3] In recent years, more systematic and concerted efforts have been made in C–H bond activation and its application in coupling chemistry. As a result exceptionally useful methods for organic synthesis have been developed, such as, the transition-metal-catalyzed functional-group-directed C–H bond functionalization to achieve C–C and C–X bonds,[4] and pioneering work by Li in the area of cross-dehydrogenative couplings (CDC), where the activation of two different C–H bonds under oxidative conditions have been achieved (Scheme 1).[5]

Organic carbamates are valuable agricultural chemicals, largely used as pesticides, fungicides, and herbicides.[6] They have also played an important role in synthetic organic chemistry, primarily as intermediates or as novel protecting groups.[7] The conventional synthesis of carbamates involves intermediates such as chloroformates or isocyanates, which in turn are prepared by employing phosgene or its substitutes.[8] To avoid the use of toxic and harmful reagents, phosgene-free routes involving the oxidative carbonylation of amines using Nobel metal catalysts have been reported.[9] The other environmentally benign route is the utilization of CO_2 as a safe and abundant reagent for the synthesis of carbamates.[10] We have been working on iodide-mediated catalytic oxidative organic transformations using TBHP as an external oxidant,[11] and in this context, we were interested to develop useful coupling protocols under oxidative conditions using transition metal and non-transition metal catalysts.



Scheme 1. a) *ortho*-Assisted C–H bond functionalization b) CDC reactions for C–C bond formation. DG = directing group.

Formamides are known to react differently under different reaction conditions. For example, Muzart summarized in his recent review that *N*,*N*-dimethylformamide (DMF), which is one of the most widely used formamide derivatives, could be a source of CO, Me_2N, Me_2NCO, oxygen, etc., depending on the reaction conditions.[12] Recent studies on the aminocarbonylation of aryl halides with DMF using transition metal catalysts have shown the possibility of the direct activation of the formamide C–H bond.[13] A few reports are available on the direct activation of the formamide C–H bond in the intermolecular addition to alkenes and alkynes.[14] Very recently, direct amidation of azoles with formamides by metal-free C–H bond activation has been achieved using *tert*-butyl perbenzoate.[15] To the best of our knowledge, this is the first report in which β-dicarbonyl- or 2-carbonyl-substituted phenols are directly coupled with *N*,*N*′-disubstituted formamides under oxidative conditions to yield carbamates (Scheme 2).

The direct coupling of formamide with aryl halides has been postulated to proceed by the Heck-type addition of aryl halides to the iminium species, which is produced from a mixture of DMF and $POCl_3$.[13a] In their recent report on the direct amidation of azoles with formamides, Wang and coworkers have proposed the possible formation of a free radical of DMF under the peroxide conditions.[15] Similarly,

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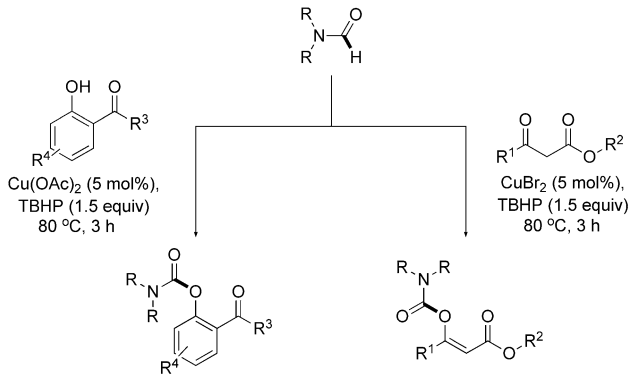
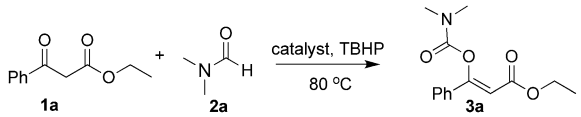


Scheme 2. Synthesis of enol and phenol carbamates by oxidative coupling. TBHP = *tert*-butyl hydroperoxide.

the copper-catalyzed oxidative coupling with peroxides has been proposed to proceed by a radical mechanism.[5] We initiated this work with the anticipation that DMF can be activated under oxidative conditions to yield the coupled product with carbon nucleophiles. For our initial experiments, ethyl benzoylacetate was chosen as the carbon nucleophile and treated with an excess of DMF, using 5 mol% of CuI as a catalyst and TBHP (70 wt% in water) as an external oxidant (Table 1, Entry 1). To our surprise, at room temperature we observed a small amount of carbamate product, in which the enol hydroxy group had participated in the oxidative coupling instead of active methylene group. This result is similar to that observed in the oxidative esterification of aldehydes to give β-dicarbonyl products.[16] Purification of the product and analysis by ^{1}H and ^{13}C NMR spectroscopy, and ESI mass spectrometry revealed that the coupled product is indeed the enol carbamate. Having observed the coupled product, optimization of the reaction conditions was carried out (Table 1). An increase in reaction temperature greatly improved the product yield (Table 1, entry 2). The absence of any coupled product in control experiments clearly shows the importance of the catalyst in this reaction (Table 1, entries 3 and 4). Both the Cu^I and Cu^{II} salts were quite active for this coupling reaction (Table 1, entry 5–12). Among the different copper salts, $CuBr_2$ provided relatively higher yields of the product. The lower activity observed with CuO could be because of the insoluble nature of the metal oxide (Table 1, entry 13). We did not observe any product formation, when one equivalent of ethyl benzoylacetate and one equivalent of DMF were reacted in a variety of solvents.[17] Next we evaluated the role of the oxidant; no product formation was observed with H_2O_2, UHP, *m*CPBA, and NaOCl as the oxidant. Further substrate screenings were done using 5 mol% of $CuBr_2$ at 80 °C with the respective formamide as the solvent and TBHP as the external oxidant (Scheme 3).

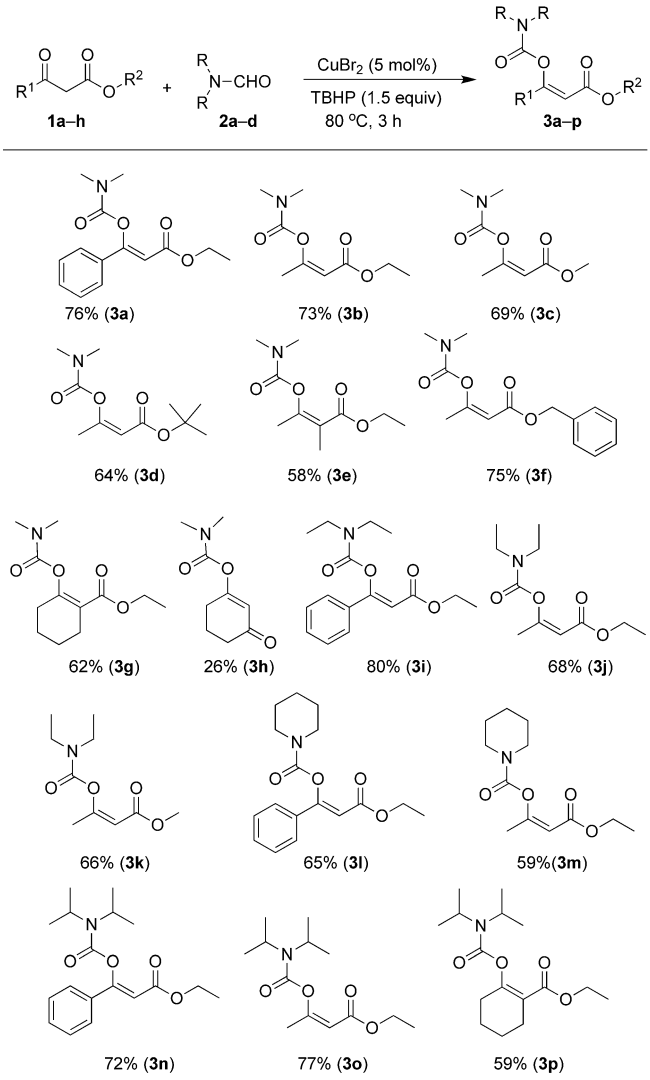
Under the standard reaction conditions, various β-ketoesters were used as substrates for the formation of enol

Table 1: Optimization of reaction conditions.[a]



Entry	Catalyst	Yield [%][b]
1	CuI	16[c]
2	CuI	67
3	–	n.r.[d]
4	CuI	n.r.[e]
5	CuBr	76
6	CuCl	78
7	CuSCN	76
8	$CuBr_2$	84
9	$CuCl_2 \cdot 2H_2O$	79
10	$Cu(ClO_4)_2 \cdot 6H_2O$	65
11	$CuSO_4 \cdot 5H_2O$	71
12	$Cu(CH_3COO)_2 \cdot H_2O$	81
13	CuO	8

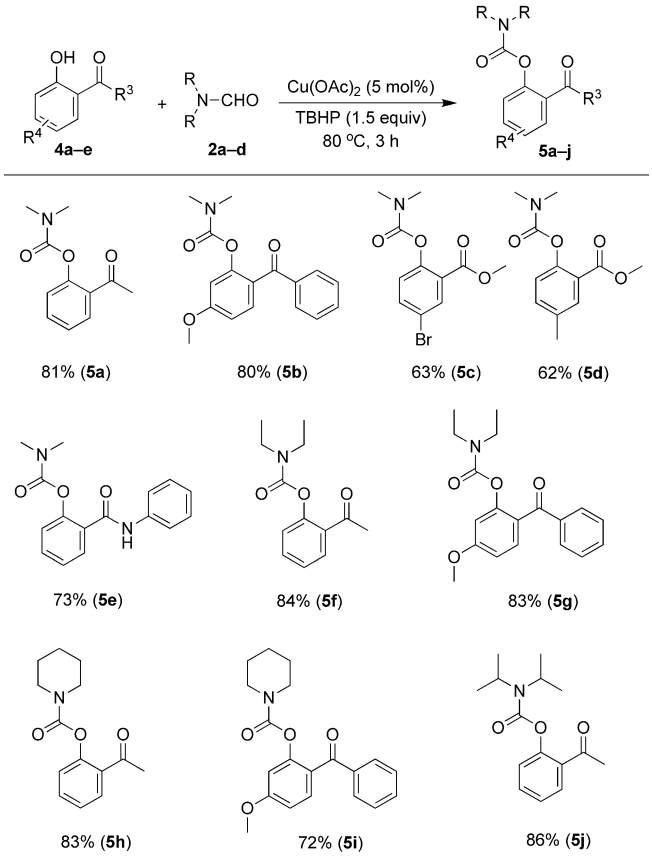
[a] Reaction conditions: **1a** (1 equiv), catalyst (5 mol%), DMF (2 mL, 27 equiv), TBHP (70 wt% in water, 1.5 equiv), 80 °C, 3 h. [b] Yields of the isolated products. [c] Reaction carried out at room temperature. [d] Without catalyst. [e] Without TBHP.



Scheme 3. Oxidative coupling of formamides with β-ketoesters.

carbamates. In general, the desired enol carbamates were obtained in good yields with high stereoselectivity towards the *Z* isomer (Scheme 3). We did not observe any *E* isomer in these reactions, as confirmed by NOE experiments of product **3c**. The nature of the β-ketoesters and dialkyl formamides did not have any profound influence on the reactivity.

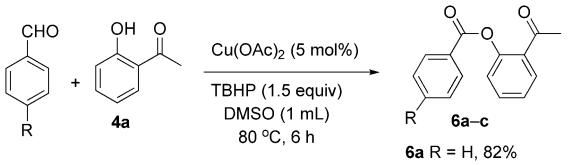
Next we looked at extending the above method to *ortho*-substituted phenolic compounds, which have structural similarities to the enol tautomer of the diketone moiety. A variety of 2-acyl and 2-benzoyl phenolic compounds, substituted with electron-withdrawing and electron-donating groups were subjected to oxidative coupling with *N*,*N*′-dialkyl formamides under the standard reaction conditions, which include 5 mol% of $Cu(OAc)_2$ as a catalyst (Scheme 4).[18] In all



Scheme 4. Oxidative coupling of formamides with phenols.

cases, we observed the formation of phenol carbamates in good yield. We did not observe any correlation between the yields and the electronic nature of the phenol substituents. This demonstrates that the substitution on the phenolic group has a negligible influence on the product conversion. Reactions of simple phenol or *p*-bromophenol with DMF did not provide the desired coupled product.

The success of the oxidative coupling of formamides with phenols having carbonyl functionality at the *ortho*-position encouraged us to investigate the corresponding oxidative esterifications with aldehydes. Generally aryl benzoates are prepared by the reaction of acyl halides, anhydrides, or activated esters with phenols. However, recently N-heterocyclic-based ligands have been successfully utilized for oxidative esterifications of aldehydes with phenols using palladium or iron catalysts.[19] Use of these ligands involves a multistep synthesis and moreover, poor yields were observed for *ortho*-substituted phenols. In the present case, the reaction between 2-acetyl phenol with various aldehydes, using DMSO as the solvent under the standard reaction conditions, provided the phenol esters in very good yields (Scheme 5).



6a R = H, 82%
6b R = Isopropyl, 80%
6c R = Cl, 79%

Scheme 5. Oxidative coupling of aldehydes with phenols.

The coordinating ability of the dicarbonyl compounds with the metal could be one of the key factors for the formation of carbamates (**3** and **5**) and esters (**6**). Moreover, the lack of the formation of any phenol carbamates (**5**) with simple phenols also supports this hypothesis. Similarly, the lack of product for the reaction between DMF and 2-acetyl phenol in the presence of the radical scavenger TEMPO, supports the hypothesis that the present coupling proceeds by a radical mechanism, which is often invoked for metal-catalyzed oxidation reactions involving peroxides. Based on these observations, we speculate that formamide radicals, analogous to the acyl radicals proposed in the copper-catalyzed oxidative esterification of aldehydes with β-dicarbonyl compounds in the presence of TBHP, could be one of the active species.[16] Moreover, the formation of such a formamide radical has been postulated recently in the direct amidation of azoles with formamides using *tert*-butyl perbenzoate as the oxidant.[15] These mechanisms are speculative and many other possible mechanisms exist, further comprehensive studies are required to elucidate the mechanism of oxidative cross-coupling chemistry involving C–H bond activations.

In summary, we have developed a novel copper-catalyzed oxidative C–O coupling reaction for the efficient synthesis of enol and phenol carbamates. Advantages of our procedure include the simplicity of operation and the fact that it is a phosgene-free route, thus avoiding the use of toxic and harmful reagents. Moreover, a high stereoselectivity was achieved for enol carbamates and the present strategy was also extended to oxidative esterification of carbonyl-substituted phenols. The scope of this reaction is under investigation and the results will be discussed in due course.

Experimental Section

General procedure: TBHP (70 wt% in water) was added dropwise, with stirring over a period of 5 min, to a mixture of β-ketoester (**1**) or phenol (**4**), copper salt (5 mol%; $CuBr_2$ for β-ketoesters and $Cu(OAc)_2$ for phenols), and formamide (2 mL). Then the reaction

temperature was increased to 80 °C and the reaction mixture was stirred for three hours. After cooling to RT, the reaction mixture was extracted with ethyl acetate and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded the crude product, which was purified by column chromatography on silica gel (ethyl acetate/hexane 1:9) to afford the required product (**3** and **5**).

A slightly modified procedure, in which DMSO was used as the solvent and the reaction time increased to 6 h, was employed for the oxidative esterification reactions resulting in the formation of product **6**.

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[17] The experiments were done with 1 mmol of ethyl benzoylacetate and 1.5 mmol DMF in 2 mL of solvent (CH_3CN, dioxane, and toluene were tested) using 5 mol % of $CuBr_2$ at 80 °C for 3 hrs. In all these cases less than 10 % of the desired products were observed.

[18] There is no strong justification for using $Cu(OAc)_2$ as the catalyst for the phenol carbamates, except that in one of the initial experiments with 2-acetyl phenol and DMF, we observed a better yield (81 %) of the product (**5a**) with $Cu(OAc)_2$ than $CuBr_2$ (75 %).

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